Cardiac hybrid imaging

Gaemperli, O ; Bengel, F M ; Kaufmann, P A

Abstract: Computed tomography coronary angiography (CTCA) and myocardial perfusion imaging techniques (single photon emission computed tomography, SPECT, or positron emission tomography, PET) are established non-invasive modalities for the diagnosis of coronary artery disease (CAD). Cardiac hybrid imaging consists of the combination (or 'fusion') of both modalities and allows obtaining complementary morphological (coronary anatomy, stenoses) and functional (myocardial perfusion) information in a single setting. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examinations for clinical effectiveness and minimization of costs and radiation dose. The feasibility and clinical value of hybrid imaging has been documented in small cohort studies and selected series of patients. Hybrid imaging appears to offer superior diagnostic and prognostic information compared with stand-alone or side-by-side interpretation of data sets. Particularly in patients with multivessel disease, the hybrid approach allows identification of flow-limiting coronary lesions and thereby provides useful information for the planning of revascularization procedures. Furthermore, integration of the detailed anatomical information from CTCA with the high molecular sensitivity of SPECT and PET may be useful to evaluate targeted molecular and cellular abnormalities in the future. While currently still restricted to specialized cardiac centres, the ongoing efforts to reduce radiation exposure and the increasing clinical interest will further pave the way for an increasing use of cardiac hybrid imaging in clinical practice.

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REVIEW

Imaging

Cardiac hybrid imaging

Oliver Gaemperli[1]*, Frank M. Bengel[2,3], and Philipp A. Kaufmann[1]

[1]Cardiac Imaging, University Hospital Zurich, Ramistrasse 100, CH-8091 Zurich, Switzerland; [2]Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, MD, USA; and [3]Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany

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Computed tomography coronary angiography (CTCA) and myocardial perfusion imaging techniques (single photon emission computed tomography, SPECT, or positron emission tomography, PET) are established non-invasive modalities for the diagnosis of coronary artery disease (CAD). Cardiac hybrid imaging consists of the combination (or 'fusion') of both modalities and allows obtaining complementary morphological (coronary anatomy, stenoses) and functional (myocardial perfusion) information in a single setting. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examinations for clinical effectiveness and minimization of costs and radiation dose. The feasibility and clinical value of hybrid imaging has been documented in small cohort studies and selected series of patients. Hybrid imaging appears to offer superior diagnostic and prognostic information compared with stand-alone or side-by-side interpretation of data sets. Particularly in patients with multivessel disease, the hybrid approach allows identification of flow-limiting coronary lesions and thereby provides useful information for the planning of revascularization procedures. Furthermore, integration of the detailed anatomical information from CTCA with the high molecular sensitivity of SPECT and PET may be useful to evaluate targeted molecular and cellular abnormalities in the future. While currently still restricted to specialized cardiac centres, the ongoing efforts to reduce radiation exposure and the increasing clinical interest will further pave the way for an increasing use of cardiac hybrid imaging in clinical practice.

Keywords Cardiac hybrid imaging • Single photon emission computed tomography • Positron emission tomography • Coronary artery disease • Molecular imaging

Coronary morphology and function—two sides of the same coin

Since the introduction of invasive coronary angiography (ICA) procedures by Sones *et al.*[1] in 1959, the diagnosis and management of coronary artery disease (CAD) has been dominated by the search for luminal narrowing and the evaluation of stenosis severity observed on angiographic films. Notwithstanding the great value of ICA over the past decades, the evaluation of coronary 'luminology' only addresses one side of the coin and fails to accurately assess the effects of luminal narrowing on myocardial blood flow. A number of landmark studies have consistently demonstrated that the angiographic severity of coronary lesions is a poor predictor of its haemodynamic relevance, and have led to a paradigm shift in CAD care, emphasizing the role of myocardial ischaemia.[2,3] In 1984, White *et al.*[4] observed a very weak correlation of stenosis severity with hyperaemic coronary blood flow measured by Doppler technique in patients undergoing coronary artery bypass graft (CABG) surgery. Ten years later, Uren demonstrated that coronary flow reserve [measured with positron emission tomography (PET)] declines with increasing stenosis severity, reaching unity at stenoses of 80% or more.[5] This relationship, however, was governed by a large scatter proving that the same degree of luminal narrowing may have varying pathophysiological effects in different individuals. Recent studies using fractional flow reserve (FFR) have shown that among stenoses of 50–90%, angiography is inaccurate in determining the haemodynamic relevance of a given lesion.[6] Similarly, a comparison study of computed tomography coronary angiography (CTCA) and myocardial perfusion single photon emission tomography (SPECT) has shown that only 32% of significant coronary stenoses ($\geq$50%) are associated with perfusion defects on SPECT (*Figure 1*).[7]

* Corresponding author. Tel: +41 44 255 35 55, Fax: +41 44 255 44 14, Email: oliver.gaemperli@usz.ch

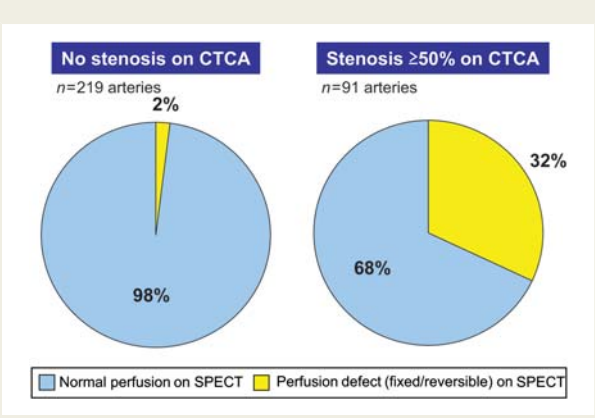

Figure 1 Functionally relevant coronary artery disease: comparison of 64-slice computed tomography coronary angiography with myocardial perfusion single photon emission computed tomography. While almost all coronary arteries without obstructive lesions were associated with a normal perfusion (left pie chart), only 32% of significant coronary stenoses (≥50%) induced a perfusion defect on SINGLE photon emission computed tomography (right pie chart). *Adapted from Gaemperli et al.*[7]

These academic observations have been confirmed by clinical studies supporting the importance of ischaemia testing for the care of stable CAD patients. The two largest randomized trials, the COURAGE and BARI-2D trials, both including patients with angiographically documented CAD, have failed to demonstrate a prognostic benefit of revascularization strategies compared with contemporary medical therapies.[8,9] A retrospective observation in >10 000 patients, however, suggests that stable CAD patients may benefit from revascularization procedures in the presence of myocardial ischaemia involving 10% or more of the left ventricular myocardium.[10] The prospective nuclear substudy of the COURAGE trial, albeit slightly underpowered to detect significant differences in cardiovascular outcomes, showed that percutaneous coronary interventions (PCIs) were more effective in reducing myocardial ischaemia than optimal medical treatment alone (−2.7 vs. −0.5%), and that the reduction in ischaemic burden was correlated with the prognosis of the patient.[11] In the randomized prospective FAME trial, measurement of FFR prior to PCI resulted in a reduction in the number of implanted stents (1.9 ± 1.3 vs. 2.7 ± 1.2) and in a significant 35% reduction in overall mortality and myocardial infarction.[12]

These data highlight the importance of assessing both sides of the coin, the presence of coronary lesions and their haemodynamic relevance, in order to offer stable CAD patients the most appropriate treatment strategy. In fact, the recently published joint revascularisation guidelines by the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgeons (EACTS) give a class I recommendation (level of evidence A) for assessing myocardial ischaemia prior to any revascularization procedure.[13] The tremendous technological evolution achieved in non-invasive imaging techniques over the last decades, including CTCA, SPECT, PET, or stress cardiac magnetic resonance (CMR) have provided cardiologists with a large non-invasive armamentarium for CAD assessment. These techniques coupled with the development of dedicated image fusion software packages to merge data sets from different modalities have paved the way for hybrid imaging.[14] In nuclear imaging, these developments have been further supported by the tremendous success of hybrid whole body PET/CT imaging in oncology. First pioneering attempts of cardiac image fusion between myocardial perfusion imaging (MPI) with SPECT and coronary arterial tree derived from ICA were promising but their widespread use was precluded by issues of the invasiveness of coronary angiography, the lack of dedicated fusion software, and often tedious and time-consuming image processing.[15,16] Today, hardware and software requirements for hybrid imaging are met by most manufacturers which provide simple platforms for introducing hybrid imaging into the clinical practice.

Computed tomography coronary angiography and myocardial perfusion imaging—suited for hybrid imaging?

Myocardial perfusion imaging

In the last three decades, myocardial perfusion SPECT has established itself as an excellent non-invasive method for the diagnosis of CAD with flow-limiting lesions with a sensitivity and specificity of 87–89% and 73–75%, respectively, depending on the choice of radionuclide and stress modality.[17] Additionally, SPECT has proved very useful for risk stratification and a wealth of data is available indicating its independent prognostic value in different clinical settings such as stable CAD, prior to non-cardiac surgery, after coronary revascularisation, and in acute coronary syndromes. Most importantly, in stable patients, a normal perfusion scan is associated with an excellent mid-term prognosis (risk of death or non-fatal MI <1% per year) even in the presence of angiographically documented CAD.[18]

Nonetheless, by nature, SPECT can only detect coronary lesions that induce perfusion defects, but does not exclude the presence of subclinical non-obstructive coronary atherosclerosis.[19,20] However, ~70% of plaque ruptures leading to myocardial infarctions occur in lesions that are non-obstructive and therefore may be missed by SPECT.[21] Indeed, large longitudinal studies in patients undergoing myocardial perfusion SPECT, have shown that a substantial proportion of patients suffering cardiac events (43% of patients suffering an acute MI and 31% succumbing to cardiac death) have normal or near-normal perfusion scans prior to their event.[22,23] Additionally, in patients with multivessel CAD, SPECT may underestimate the true extent of disease, since likelihood of detection is highest with culprit lesions but lower with other milder lesions.[24–26] Balanced reduction in myocardial hyperaemic blood flow is probably rather rare but it may explain paradoxical underestimation of clinical risk in high-risk cohorts with a normal or near-normal SPECT. Finally, particularly in obese subjects, SPECT is prone to false-positive results due to non-uniform photon attenuation.[27]

Positron emission tomography has higher spatial and temporal resolution than SPECT and, due to more robust methods of

attenuation correction, allows quantification of resting and hyperaemic regional myocardial perfusion. Quantification of regional perfusion appears to be useful in patients with diffuse CAD or balanced disease where the relative assessment of myocardial perfusion by SPECT may fail in uncovering true perfusion changes.[25] A recent review reports a high weighted sensitivity and specificity of 90 and 89%, respectively, and smaller comparisons with SPECT suggest a higher diagnostic accuracy for PET.[28] Several series with ^{82}Rb PET reported an incremental contribution to prognostication by the addition of measurement of changes in the ejection fraction, improving the identification of multivessel CAD.[29] Clinical circumstances in which PET may be particularly preferable to SPECT include obese patients with high soft tissue attenuation and patients with a higher pre-test likelihood of multivessel CAD.

Computed tomography coronary angiography

On the other hand, CTCA has advanced over the past years as the most accurate tool for noninvasive coronary angiography. Current multi-slice devices coupled with improved acquisition protocols allow robust and reproducible assessment of coronary morphology with high temporal and spatial resolution at low radiation exposure.[30,31] The diagnostic performance of CTCA compared with ICA has been evaluated in over 45 single-centre studies.[32] Recently, three multi-centre studies have demonstrated the high diagnostic accuracy of 64-slice CTCA with a sensitivity and specificity of 85–99% and 64–90%, respectively, and very low rates of non-evaluable scans.[33–35] Particularly, the high negative predictive value (NPV) which is close to 100% has positioned CTCA as an excellent tool for ruling out the presence of CAD in patients with low to intermediate pre-test probability.[36]

Nonetheless, despite its high diagnostic accuracy, CTCA remains a purely anatomical technique, and very much like ICA, is poor at predicting the haemodynamic relevance of stenoses.[7,19] However, besides delineation of the coronary lumen, CTCA also allows visualization of the coronary vessel wall, thereby providing valuable information on the presence of eccentric non-obstructive plaques as well as plaque size, composition, calcifications, and vascular remodelling.[37] Although the clinical significance of these parameters is still under intense investigation, evidence is accumulating for an incremental prognostic value of detecting non-obstructive coronary plaques over the presence of coronary stenoses in stable CAD patients. Van Werkhoven showed that the presence of non-calcified (so-called soft plaques with presumably high-lipid

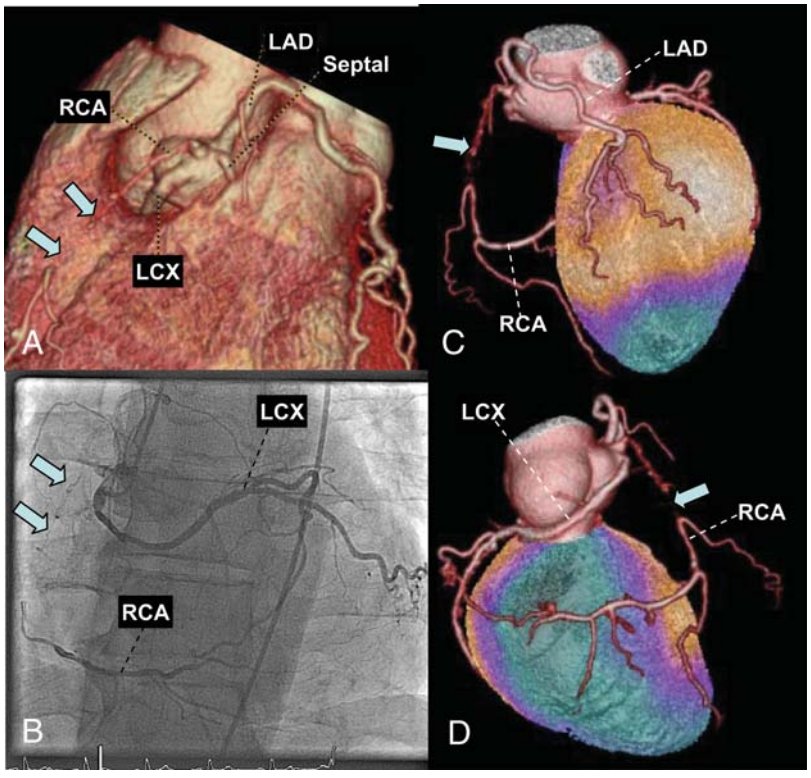

Figure 2 Fifty-four-year-old patient with a congenital coronary anomaly consisting of a common origin of all four coronary arteries (left anterior descending, septal branch (septal), right coronary artery, and left circumfley artery) from the right coronary ostium (*A*). The invasive coronary angiography (*B*) shows selectively the retroaortic course of the left circumflex and collaterals to the occluded right coronary artery (arrows). On hybrid single photon emission computed tomography/computed tomography imaging (*C* and *D*), a fixed perfusion defect can be appreciated in the territory of the occluded right coronary artery (arrows). The left anterior descending artery runs anterior to the pulmonary trunk, and the septal branch runs on an interarterial course between pulmonary trunk and ascending aorta to the septal wall.

content) provided incremental prognostic information over the presence of obstructive lesions, and clinical variables.[38] In a prospective study by Motoyama[39], low CT plaque attenuation (<30 Hounsfield units) and positive vessel remodelling were identified as strong predictors of future acute ischaemic events. These findings support the notion that non-obstructive coronary lesions, despite having no effect on myocardial perfusion, may harbour the risk for rupture and subsequent vessel thrombosis. Thus, CTCA has a complementary role to myocardial perfusion SPECT and represents an ideal partner modality for hybrid imaging.

Hybrid imaging—nice to have or truly needed?

The incremental value of hybrid cardiac imaging resides in the accurate spatial co-localization of myocardial perfusion defects and subtending coronary arteries (*Figure 2*). Traditionally, this integration process is mentally performed by using a standardized myocardial segmentation model that allocates each segment to one of the three main coronary arteries, thereby defining standardized myocardial vascular territories.[40] However, coronary artery anatomy varies considerably among individuals, and disagrees with standardized vascular territories in a significant proportion of patients, particularly in the vascular territories of the left circumflex (LCX) and right coronary artery (RCA). In a recent study, Javadi *et al.*[41] compared standardized myocardial vascular territories with individual coregistered myocardial territories using ^{82}Rb PET/CTCA and found disagreement in 9% of all segments. Notably, in 72% of all patients, a disagreement in at least one myocardial segment was found. Most frequently, standard right coronary segments were reassigned to the LCX territory (39% of reassigned segments), and standard circumflex segments were reassigned to the left anterior descending territory (30%) (*Figure 3*). The validity of segmental assignment with hybrid PET/CTCA was tested by comparison with *ex vivo* Monastral Blue dye staining in dogs with experimental coronary stenoses and has yielded an excellent agreement (kappa 0.80).

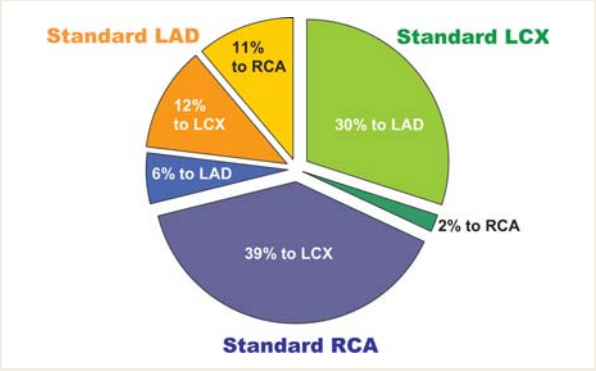

Figure 3 Percentages of reassigned myocardial segments after individual review of hybrid positron emission tomography/computed tomography images. Standardized myocardial assignment is shown by colour. Most frequently, standard right coronary segments were reassigned to the left circumflex territory (39% of reassigned segments), and standard circumflex segments were reassigned to the left anterior descending territory (30%). *Adapted from Javadi et al.*[41] *with permission of the Society of Nuclear Medicine.*

Clinical value of hybrid imaging

Table 1 shows a summary of clinical studies evaluating the diagnostic performance of cardiac hybrid imaging. The feasibility and clinical robustness of non-invasive hybrid imaging was first documented by Namdar *et al.* in a clinical study involving fusion of ^{13}N–NH_3 PET with 4-slice CTCA in 25 patients with CAD.[42] The hybrid PET/CTCA images allowed to identify flow-limiting coronary lesions which required a revascularization procedure (as defined by ICA and PET) with a sensitivity, specificity, positive predictive value (PPV), and NPV of 90, 98, 82, and 99%, respectively. These encouraging results were confirmed by a similar study with SPECT/CTCA showing that the hybrid approach resulted in a significant improvement in specificity (from 63 to 95%) and PPV (from 31 to 77%) compared with CTCA alone for detecting flow-limiting coronary stenoses.[43] A similar diagnostic performance was reported by Groves *et al.*[44]

Table 1 Diagnostic accuracy of cardiac hybrid imaging (SPECT/CTCA and PET/CTCA) (Vessel-based analysis)

Author	Hybrid system	*n*	Gold standard (definition of significant CAD)	Sens	Spec	PPV	NPV
Namdar *et al.*[42]	^{13}N–NH_3 PET/4-slice CTCA	25	Flow-limiting coronary stenoses requiring revascularization (ICA + PET)	90	98	82	99
Rispler *et al.*[43]	SPECT/16-slice CTCA	56	Flow-limiting coronary stenoses (>50% stenosis on ICA + SPECT pos.)	96	95	77	99
Groves *et al.*[44]	^{82}Rb PET/64-slice CTCA	33	>50% stenosis on ICA	88	100	97	99
Sato *et al.*[45]	SPECT/64-slice CTCA[a]	130	>50% stenosis on ICA	94	92	85	97
Kajander *et al.*[46]	^{15}O–H_2O PET/64-slice CTCA	107	Flow-limiting coronary stenosis (>50% stenosis of ICA + FFR)	93	99	96	99

n denotes the number of patients in each study; SPECT, single photon emission computed tomography; CTCA, CT coronary angiography; PET, positron emission tomography; CAD, coronary artery disease; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; ICA, invasive coronary angiography; FFR, fractional flow reserve.
[a]Hybrid SPECT/CTCA only applied for non-evaluable arteries on CTCA (14%).

Table 2 Incremental clinical value of fused hybrid imaging compared to the side-by-side analysis

Author	Hybrid system	Patient population	Incremental value of fused hybrid imaging
Gaemperli *et al.*[47]	SPECT/64-slice CTCA and 3D image fusion	38 patients with ≥1 SPECT defects	Modification of initial interpretation in 29% of patients In equivocal lesions, haemodynamic relevance could be confirmed in 35% and excluded in 25%
Santana *et al.*[48]	16- and 64-slice CTCA and MPI (SPECT or ^{82}Rb PET)	50 patients with suspected CAD	Modification of initial interpretation in 28% of patients Trend towards increased sensitivity (by 17%) in patients with multivessel disease
Slomka *et al.*[49]	Motion-frozen SPECT/64-slice CTCA (automatic coregistration)	35 patients with suspected CAD	Improved diagnostic performance in RCA- and LCX-territories

SPECT denotes single photon emission computed tomography; CTCA, CT coronary angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; CAD, coronary artery disease.

using an ^{82}Rb PET/CT hybrid system. Sato *et al.*[45] showed that adding SPECT information in non-evaluable arteries on CTCA improved particularly specificity and PPV of the latter techniques significantly (from 80 to 92%, and from 69 to 85%, respectively). Notably, the majority of non-evaluable severely calcified vessels in the left anterior descending artery were positive on stress nuclear MPI, whereas the majority of non-evaluable vessels with motion artefacts in the RCA were negative. One of the largest, recently published studies included 107 patients undergoing hybrid $^{15}O-H_2O$ PET/64slice-CTCA.[46] In this study, haemodynamic significance of ICA stenoses was confirmed in 18 of 40 patients with FFR providing a more comprehensive gold standard. Consequently, the use of PET/CTCA increased the PPV significantly from 76 to 96% compared with CTCA alone.

However, a number of limitations apply to the aforementioned studies, including the limited number of patients, the variety of hybrid systems used, and the lack of a uniform gold standard. Three studies have specifically addressed the incremental value of hybrid cardiac imaging over the side-by-side analysis of CTCA and myocardial perfusion images (*Table 2*). In the first report of 38 patients with perfusion defects on SPECT, the number of lesions with equivocal haemodynamic relevance was significantly reduced using SPECT/CTCA fusion compared with the side-by-side analysis.[47] Among these equivocal lesions the hybrid approach confirmed haemodynamic significance in 35% and excluded it in 25%. This added clinical value could be observed in 29% of all patients, and was particularly common in patients with multivessel disease and intermediate severity stenoses or in patients with diseased side branches. Santana *et al.*[48] showed a significantly higher diagnostic performance for fused SPECT/CTCA imaging compared with SPECT alone ($P < 0.001$) and to the side-by-side analysis of SPECT and CTCA ($P = 0.007$) for the diagnosis of obstructive CAD on ICA. Interestingly, this improved diagnostic performance was mainly a result of a higher sensitivity in patients with multivessel disease. A recent study implementing motion-frozen SPECT data and CTCA-guided SPECT contour and territory adjustments found that the improved diagnostic value of hybrid imaging was mainly driven by higher diagnostic indices in LCX and RCA territories.[49]

Table 3 Incremental clinical value of hybrid imaging in the diagnosis of coronary artery disease

- Improved diagnostic performance to detect CAD compared with SPECT of CTCA alone
- Allows to identify flow-limiting coronary lesions ('culprit lesions') requiring revascularization (particularly in the RCA- and LCX-territory and with multivessel disease)
- Adds diagnostic information in approximately one-third of patients
- Provides independent prognostic information through combination of morphological and functional criteria

Hence, hybrid cardiac imaging may facilitate the identification of haemodynamically significant coronary artery stenoses and thereby guide clinicians on the appropriate method of revascularization. Moreover, in intermediate stenoses, a hybrid study may accurately confirm or rule out their haemodynamic significance and thereby reduce the number of potentially unnecessary stent implantations, a key cost driver in cardiovascular medicine. A recent study including >500 patients has also documented the prognostic value of hybrid imaging.[38] In this study, CTCA provided independent prognostic information over SPECT alone. Most importantly, in patients with a normal SPECT study, an abnormal CTCA scan was associated with a higher rate of the combined endpoint, and therefore warrants more aggressive risk factor modification. These observations lend further support to the notion that stable CAD patients should undergo a comprehensive assessment of both myocardial perfusion and coronary morphology in order to fully apprehend their coronary risk and assist in the choice of the most appropriate treatment strategy. Nonetheless, it should be noted that evidence to support these assumptions is still scarce and just beginning to accrue. Further studies are needed to document an effect of hybrid imaging on treatment strategies, and to assess whether changes in treatment based on hybrid imaging may have an impact on the patients' prognosis. Results of ongoing prospective multicentre trials, such as SPARC, EVINCI and PROMISE, are therefore eagerly awaited and will hopefully shed more light into the future of cardiac hybrid imaging.[50,51]

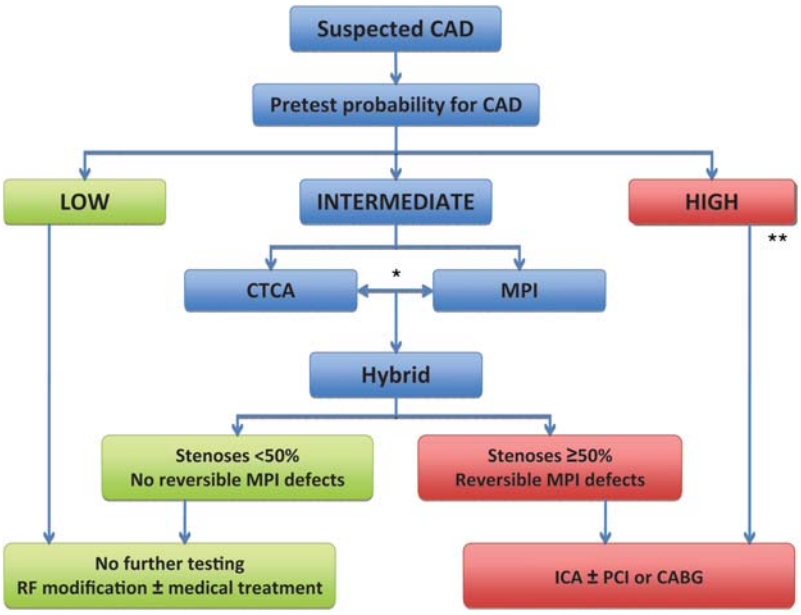

Figure 4 Proposed clinical algorithm for the use of hybrid imaging in the diagnosis of coronary artery disease. *A second non-invasive test may be performed if the first test was inconclusive or equivocal. **Myocardial perfusions imaging may be performed in high pre-test probability patients to localize ischaemia. CTCA denotes CT coronary angiography; MPI, myocardial perfusions imaging; RF, risk factor; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. *Adapted from Flotats et al.*[55]

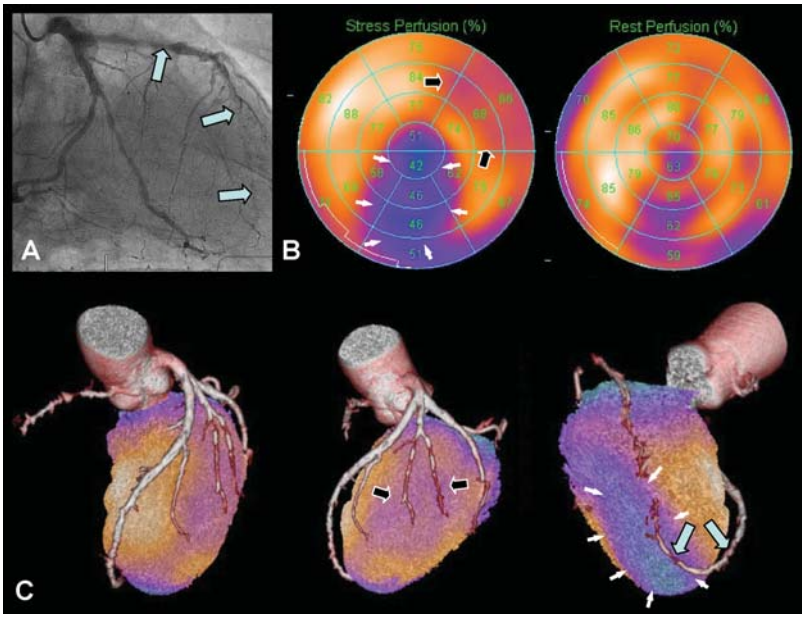

Figure 5 Eighty-six-year-old patient with increasing angina at rest. The invasive coronary angiography (*A*) demonstrates a left dominance with severely calcified vessels. The left anterior descending coronary artery shows a proximal 50–70% stenosis and a distal long functional occlusion (solid blue arrows). The intermediary branch is functionally occluded. The left circumflex artery shows a proximal 50% stenosis. On single photon emission computed tomography (*B*), a large inferior (small white arrows) and a faint anterolateral ischaemia (solid black arrows) can be observed. The hybrid single photon emission computed tomography/computed tomography coronary angiography reconstructions (*C*) highlight the dominance of the left anterior descending artery (solid blue arrows), which turns at the apex to supply the majority of the inferior wall and is responsible for the large ischaemia (small white arrows). Additionally, the anterolateral ischaemia can be assigned to the intermediary branch (solid black arrows).

Role of coronary artery calcium scoring for hybrid imaging

A large body of evidence has established coronary artery calcium scoring (CACS) as a strong predictor of cardiovascular events in asymptomatic subjects.[52] Besides its prognostic value, the CACS can also be used for diagnostic purposes in symptomatic patients. A number of studies have addressed the added diagnostic and prognostic value of CACS combined with MPI, due to the relative ease to obtain CACS images (no contrast injection and low overall radiation exposure). This approach is further promoted by the increasing availability of hybrid scanners integrating low- or high-end CT devices with SPECT cameras). In a recent study by Schepis *et al.*,[53] 77 symptomatic patients with intermediate coronary risk (based on a 10-year Framingham risk for death or non-fatal MI of 10–20%) underwent SPECT, CACS, and ICA for suspected CAD. The added use of CACS (at a cut-off of 709 Agatston units) increased the sensitivity of SPECT from 76 to 86% and NPV from 76 to 83%. Thus, adding CACS to SPECT may allow detecting patients with extensive multivessel disease, which, despite normal perfusion on SPECT, may have a paradoxical high long-term coronary risk.[54]

Schenker *et al.*[54] first documented an added and independent prognostic value of CACS combined with MPI. In a prospective follow-up study including 695 consecutive patients with intermediate clinical risk undergoing CACS and ^{82}Rb perfusion PET, the authors observed a stepwise increase in death and MI rates with increasing CACS in patients with and without ischaemia. Among patients with normal perfusion, the annualized event rate in patients with a CACS of 0 was lower than in those with a CAC score $\geq$1000 (2.6 vs. 12.3%, respectively). Likewise, in patients with ischaemia on PET, the annualized event rate in those with a CACS of 0 was lower than among patients with a CAC score $\geq$1000 (8.2 vs. 22.1%).

How to implement cardiac hybrid imaging into current algorithms

Table 3 summarizes the most important clinical aspects of cardiac hybrid imaging. Current evidence described above suggests that hybrid imaging may be particularly useful in the following subgroups of patients: Patients with multivessel disease or perfusion defects involving the inferior and lateral wall, and patients in which either CTCA or MPI yields inconclusive or equivocal results. In the latter group, the second test is performed to exclude or confirm a potentially pathological finding in the first test according to a protocol of 'serial testing'. The second test therefore plays the role of an additional gatekeeper of ICA and fusion of images is performed 'on-the-go' (*Figure 4*). Although in the majority of cases, separate analysis of data sets largely serves the purpose of gatekeeping, fusion of images is recommended as clinical information can be enhanced in almost one-third of patients (*Table 3*). In the former group, hybrid imaging is performed to allocate perfusion defects to their corresponding coronary artery and guide revascularization strategies. Often, patients are referred after diagnostic ICA, in which the culprit lesion is unclear and the difficult anatomy of the lesions (calcified long or bifurcated lesions, chronic total occlusions, tortuous vessels) is a deterrent to *ad hoc* PCI (*Figure 5*). This approach allows to confirm the haemodynamic significance of a given lesion before embarking in tedious and potentially harmful revascularization attempts, and provides a platform for multidisciplinary coronary teams including an interventional cardiologist and a cardiac surgeon to discuss the most appropriate treatment strategy (medical conservative vs. percutaneous vs. surgical revascularization).

Table 4 Estimated effective radiation dose from cardiac diagnostic imaging

Protocol	Injected activity (MBq)[a]	Effective dose (mSv)
^{99m}Tc sestamibi 1-day stress/rest	350/1000	11.3
^{99m}Tc sestamibi 2-day stress/rest	950/950	15.7
^{99m}Tc tetrofosmin 1-day stress/rest	320/960	9.3
^{99m}Tc tetrofosmin 2-day stress/rest	950/950	12.8
^{201}Tl stress/redistribution	130	22.0
^{201}Tl stress/reinjection	55/110	31.4
^{82}Rb stress/rest[72]	1850/1850	4.6
^{13}N–NH_3 stress/rest	550/550	2.4
^{15}O–H_2O stress/rest	1100/1100	2.5
^{18}F-fluorodeoxyglucose (viability)	350	7.0
CAC-scan (prospective ECG-triggering)[73]		1.0
CAC-scan (retrospective ECG-triggering)[73]		3.0
4-slice CTCA (without tube current modulation)		6.7–13.0
4-slice CTCA (with tube current modulation)		2.5–6.2
16-slice CTCA (without tube current modulation)		4.9–20.6
16-slice CTCA (with tube current modulation)		4.3–8.1
64-slice CTCA (without tube current modulation)		8.0–21.4
64-slice CTCA (with tube current modulation)		7.0–14.0
64-slice CTCA (prospective ECG-triggering)[30]		2.1
320-slice CTCA (prospective ECG-triggering)[74]		6.8
2 × 128-slice (dual source), high pitch spiral-CTCA[58]		0.9
Diagnostic coronary angiography		2.3–22.7

Adapted from Einstein *et al.*[56]
[a]Effective radiation doses are estimated using ICRP publication 60 tissue weighting factors.[75]
CAC denotes coronary artery calcium; CTCA, CT coronary angiography; ECG, electrocardiogram.

Recently, a joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR), and the European Council of Nuclear Cardiology (ECNC) have given recommendations on the appropriate use of cardiac hybrid imaging.[55] The statement supports its use in patients with an intermediate pre-test probability of CAD and acknowledges its potential as a promising cardiac non-invasive imaging tool. It is also noted, however, that the clinical impact and the incremental value of hybrid imaging need to be evaluated in larger cohorts and multicentre investigations. As mentioned above, data are still lacking on the impact of hybrid imaging on management strategies, cardiovascular outcomes, and cost-effectiveness.

Radiation exposure

Positron emission tomography, SPECT, and CT are diagnostic modalities that use ionizing radiation to generate images of anatomical structures. The widely accepted 'Linear-No-Threshold' (LNT)-theory describes a linear relationship between radiation dose and radiation-induced stochastic effects (particularly cancer risk). In fact, depending on image modality, choice of radionuclide, and protocol, radiation exposure from medical imaging may vary considerably, and early studies with 64-slice CTCA report total effective radiation doses of up to 21.4 mSv.[56] However, improvements in image acquisition protocols, particularly the introduction of ECG-driven tube current modulation, body-mass-index-adapted tube voltage modulation, and prospective ECG-triggered sequential scanning have achieved ~30–90% reductions in patient radiation exposure.[30,57] The most recent high-pitch scanning protocols using dual-source CT scanners have even lowered doses into the sub-milli-Sievert range (*Table 4*).[58]

Similarly, myocardial perfusion SPECT using ^{102}Thallium may reach effective radiation doses up to 20–30 mSv. Shorter-lived perfusion tracers based on ^{99m}Technetium (^{99m}Tc) allow much lower radiation exposure in the range of 9.3 mSv for a full 1-day stress/rest study. The current introduction of solid-state detectors based on cadmium–zinc–telluride alloy may allow to further reduce radiation exposure by means of a higher detector sensitivity and improved energy resolution.[59] Moreover, some of the currently used cyclotron-dependent perfusions tracers for PET imaging (i.e. $^{15}O–H_2O$ and $^{13}N–NH_3$) are associated with even lower radiation doses and may therefore be particularly suitable for hybrid imaging (*Table 4*).[42,46]

Recent years have witnessed an explosion in the use of medical imaging procedures which has subsequently shifted the focus on aspects of patient safety and radiation risks.[60] Current efforts are directed towards reducing radiation exposure from medical imaging while maintaining a high level of image quality and diagnostic performance. Particularly, in the field of cardiac non-invasive imaging, impressive reductions in patient radiation exposure have been achieved through optimized image acquisition protocols and a more advanced generation of scanners thereby promoting the use of hybrid technologies in clinical practice.[30] In fact, a recent report has documented the feasibility of stress-only SPECT/CTCA hybrid studies with a cumulative radiation dose of 5.4 mSv.[61]

Future perspectives—hybrid imaging using molecular targets

Radionuclide imaging is increasingly contributing to the development of imaging strategies which go beyond the assessment of myocardial perfusion, towards characterization of molecular events on the tissue level. Cardiovascular molecular imaging aims at the visualization of specific molecules and pathways that precede or underlie changes in morphology, physiology, and function. Examples are the use of neuronal imaging to identify subjects

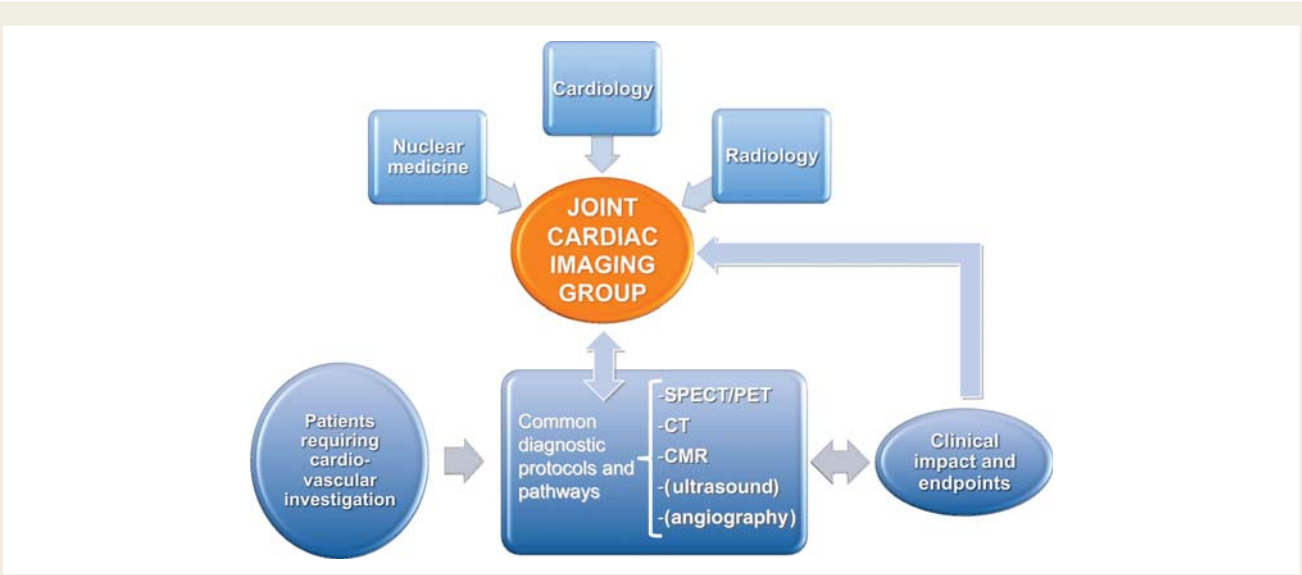

Figure 6 Fusion beyond images. Possible organization of joint multi-disciplinary diagnostic services. *Reprinted from Fraser et al.*[71] *with permission of Oxford University Press.*

at risk for ventricular arrhythmia,[62,63] the development of compounds targeting plaque vulnerability before rupture and subsequent myocardial infarction,[64,65] and the targeting of biomechanisms which precede left ventricular remodelling and heart failure development.[66,67] Additionally, molecular imaging has great potential to facilitate the discovery and development of novel therapies through improved target identification and implementation of more efficient endpoints, as well as visualization of cellular and subcellular target structures. Examples are the development of reporter gene imaging techniques,[68] and the implementation of cell labelling for imaging of engraftment after transplantation.[69] This need to visualize small amounts of molecular-targeted compounds in small target areas will not only drive advances in the imaging sciences such as in instrumentation, reconstruction algorithms and probe design in order to improve the detection sensitivity, molecular specificity, and translational potential. It also provides a strong rationale for hybrid imaging approaches, where the nuclear imaging component is used for molecular targeting and the CT is used for localization of the molecular signal.[70]

Conclusions

Through integration and spatial co-localization of morphological and functional information, hybrid imaging appears to offer superior diagnostic and prognostic information compared with stand-alone or side-by-side interpretation of data sets. Particularly in patients with multivessel disease and/or perfusion defects in inferolateral myocardial territories, the hybrid approach allows identification of flow-limiting coronary lesions and thereby provides useful information for the planning of revascularization procedures. However, the clinical impact and incremental value of integrated imaging need to be evaluated and confirmed in larger cohorts and multicentre investigations. Furthermore, integration of the detailed anatomical information from CTCA with the high molecular sensitivity inherent with SPECT and PET may be useful to evaluate targeted molecular and cellular abnormalities in the future. It is foreseeable that the appropriate use of alternative and complementary tests will require their integration into joint clinical diagnostic services where experts in all methods collaborate (*Figure 6*).[71] This process will be supported by a shift from specializing in a particular technique that is applied by cross-sectional imaging to multiple organs, to an organ or system-based approach where the diagnostic expert is more concerned with function, the integration of results into clinical decision-making, and the impact of diagnostic imaging on clinical outcomes.

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